REVIEW ARTICLE

Drug Safety 1999; 21 Suppl. 1: 69-80
0114-5916/99/0001-0069/$06.00/0

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Cardiac Effects of Ebastine and Other Antihistamines in Humans

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Abstract

The electrocardiographic effects of ebastine and its active metabolite, carebastine, have been studied alone and in relevant drug-interaction studies in various patient populations. The overall cardiac tolerability of ebastine is excellent. In ebastine dose-ranging studies in adults and children, there were no meaningful dose-related changes in the QTc interval. At high doses of ebastine (5 to 10 times the recommended dose), a modest 10.3 msec increase in QTc was observed. Recommended doses of ebastine had no meaningful effect on QTc in the elderly or in patients with renal or hepatic insufficiency. Interaction studies involving ebastine with ketoconazole revealed a significant increase in the serum ebastine concentration and in the elimination half-life of ebastine, with a modest 18.1 msec increase in QTc (approximately 10 msec above ketoconazole alone) and a plateau QTc-ebastine relationship at higher ebastine levels. Similar, though more minor, QTc findings were observed during coadministration of ebastine with erythromycin. No QTc effects were noted when ebastine was administered with theophylline, and the QTc was similar when ebastine was administered with or without food. These findings indicate that ebastine is well tolerated and, in contrast to terfenadine and astemizole, has no clinically meaningful effect on the QTc interval even at high serum concentrations. As with other 'safe' antihistamines, which have shown similar modest increases in QTc when coadministered with ketoconazole, caution should be exercised when administering ebastine to patients having the long QT syndrome or hypokalaemia, and in patients receiving azole antifungals or macrolide antibacterials.

1. Introduction

The first reports of cases of torsade de pointes associated with terfenadine treatment in humans were rapidly followed by demonstrations of blockade of cardiac potassium channels, delays in the repolarisation phase of the action potential and prolongations of the QTc interval in the ECG in nonclinical models. These provided a readily acceptable explanation of this phenomenon, which was also shown to be associated with the presence of high serum concentrations of unmetabolised drug.[1]

The finding of similar effects with astemizole[1] supported this explanation of why these antihistamines were associated with torsade de pointes. The extreme rarity of such drug-induced arrhythmias, which require enormous patient exposure for their

detection, led to a variety of experimental models being suggested and used for screening drugs for potential arrhythmogenicity in humans.

Unfortunately, whereas terfenadine and astemizole are potently active in every one of these models, the other nonsedative antihistamines and/or their metabolites are active in only 1 or 2 models, and, moreover, in different models for different antihistamines. This lack of consistency between the models used, together with the high doses/concentrations needed to demonstrate activity compared with those of terfenadine and astemizole, makes interpretation of the data difficult and unreliable in terms of extrapolation to clinical risk for these other antihistamines.

In the case of ebastine and its active metabolite, carebastine, neither compound (3 μmol/L) prolonged action potentials in guinea-pig isolated papillary muscle[2] or blocked the human Kv1.5 channel[3] *in vitro*. Whereas carebastine (3 μmol/L), but not ebastine, produced some minor prolongation of the action potential in rabbit Purkinje fibres,[4,5] the reverse situation was found for inhibitory effects on the *HERG (*human erg-related gene) potassium channel (personal communication).[6]

In vivo, oral (rat and dog) or intracoronary (dog) administration of either compound was without effect on cardiovascular parameters, including the ECG,[7,8] whereas high (10 to 50 mg/kg) intravenous doses of ebastine, but not carebastine, prolonged the QTc interval in anaesthetised guinea-pigs.[9]

Which, if any, of these different models should or could be used to predict the arrhythmogenic proclivity or tolerability of ebastine is clearly a subject for endless debate. Even in those few studies where positive effects have been found, this has only been at concentrations/doses markedly higher than those required to show similar effects with terfenadine or astemizole.

In any event, the problem of extrapolation of preclinical electrophysiological findings to clinical practice is clearly obviated by the use of electrocardiographic measurement in humans. With ebastine, this has been carried out not only during routine trials for efficacy and tolerability, but also in specific clinical pharmacology studies under conditions of overdose and metabolic inhibition.

2. Cardiac Tolerability Data from Efficacy and Tolerability Clinical Trials

2.1 Adults

During the clinical development of ebastine, 12-lead ECGs and Holter monitoring (which was optional) were recorded from 5 multicentre, placebo-controlled, double-blind studies in adult patients with seasonal or perennial allergic rhinitis.[10] Measurements were performed at baseline and weekly during the treatment periods, at 3 to 5 hours postdose, which approximates the time to reach maximum plasma concentrations (t_{max}) of carebastine.

All ECGs were read by a central laboratory and the QTc interval was calculated from lead II by use of Bazett's formula. Pooled data showed that 1202 patients (842 receiving ebastine and 360 receiving placebo) had both baseline and double-blind ECGs. 715 patients (59.5%) were male and 487 (40.5%) were female, the majority (91.6%) were Caucasian, and the mean age was 30 years (range 12 to 77 years). The dosage of ebastine was 1 to 30mg daily for 2 to 3 weeks (predominantly 10 and 20mg), except in 74 patients who were treated with 10mg twice daily. There were no direct correlations between any of the demographic variables and QTc interval duration.

A t-test was used to compare the mean observed QTc for each dosage group with the mean for placebo, and the only statistically significant difference found was that the maximum QTc for placebo was greater than that of the 10mg daily group. Despite the obvious implication of a shortening rather than a prolongation of the QTc interval, this finding was considered to be a statistical artefact rather than a true effect of ebastine. There was no dose-related response in the QTc interval from 1 to 30mg of ebastine, and categorical changes in maximum values or percentage increases were virtually identical in the ebastine- and placebo-treated patients (table I). It is important to note that these values are

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Table I. Summary of maximum observed QTc interval (Bazett's correction) and percentage change in QTc interval from pooled clinical trials of ebastine administered once or twice daily to adults, and once daily to children aged 6 to 12 years. The QTc values used are from single time-point measurements and are not the means of serial measurements made at set intervals during the day as in tables II, III and IV. As such, they are subject to a spontaneous background diurnal variation of up to 100 msec.[11,12] (Adapted from Moss et al.,[13] with permission from Blackwell Science Ltd)

Treatment	No. of patients	Maximum QTc value with ebastine [no. of patients (%)]		Increase in QTc from baseline [no. of patients (%)]	
		<444 msec	444-499 msec	<15%	15-24%
Adults					
1mg qd	17	16 (94.1)	1 (5.9)	17 (100.0)	0 (0)
3mg qd	19	19 (100.0)	0 (0)	18 (94.7)	1 (5.3)
10mg qd	272	261 (96.0)	11 (4.0)	269 (98.9)	3 (1.1)
10mg bid	74	66 (89.2)	8 (10.8)	73 (98.7)	1 (1.3)
20mg qd	444	408 (91.9)	36 (8.1)	433 (97.5)	11 (2.5)
30mg qd	16	14 (87.5)	2 (12.5)	16 (100.0)	0 (0.0)
Ebastine total	842	784 (93.1)	58 (6.9)	826 (98.0)	16 (1.9)
Placebo	360	339 (94.2)	21 (5.8)	355 (98.6)	5 (1.4)
		<454 msec[a]	454-499 msec	<15%	>15-25%
Children					
1mg qd	9	9 (100)	0 (0)	9 (100)	0 (0)
5mg qd	186	180 (96.8)	6 (3.2)	179 (96.2)	7 (3.8)
10mg qd	7	7 (100)	0 (0)	7 (100)	0 (0)
Ebastine total	202	197 (97.5)	6 (2.5)	195 (96.5)	7 (3.5)
Placebo	178	168 (94.4)	10 (5.6)	177 (99.4)	1 (0.6)

a A categorical threshold QTc value of 454 msec was used in all studies in children, instead of 444 msec in adults, since children have higher QTc values compared with adults.

bid = twice daily; **qd** = once daily.

from single time-point measurements and, as such, are subject to spontaneous background diurnal variation of up to 100 msec.[11,12]

Similarly, there were no clinically relevant findings in any of the 226 patients who had 24-hour Holter monitoring at baseline and the end of the study, nor were there any serious adverse events in these patients.

2.2 Children

Correspondingly, no electrocardiographic effects were seen in the pooled data from clinical efficacy and tolerability studies in 202 children aged 6 to 12 years treated with ebastine 1 to 10mg daily (table I). As in the adult data, these values are from single time-point measurements.

3. Cardiac Tolerability Data from Clinical Pharmacology Trials

3.1 High Doses of Ebastine

Two studies were conducted to evaluate the effects of high doses of ebastine on the QTc interval. In the first study, 56 participants were randomised into groups of 14 to receive ebastine 10, 20 and 40mg or placebo, and, during a separate time-period, a further 14 participants received ebastine 80mg and 7 received placebo.[14]

ECGs were performed serially up to 24 hours at baseline and on days 1, 5, 6, 7 and 8. The mean QTc changes from baseline on day 8 were 7 and 12, 14, 20 and 12 msec for placebo and ebastine 10, 20, 40 and 80mg, respectively. The data demonstrated no consistent effect of ebastine on the QTc interval. At steady state, the change was statistically significant for ebastine 40mg, but not for 80mg, when compared with placebo. Linear regression analysis showed no relationship between the QTc interval or the QTc interval change from baseline and plasma ebastine or carebastine concentrations. Since these data were difficult to interpret, a second high dose cardiac tolerability study was conducted to compare the electrocardiographic effects of ebastine 60 and 100mg daily for 7 days (recommended dosages are 10 and 20 mg/day) with those of placebo and terfenadine 180mg twice daily for

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Table II. Comparison of the effects of 7 days' administration of placebo, ebastine and terfenadine on the mean, maximum and area under curve for the first 12 hours (AUC_{0-12h}) QTc intervals (msec) in a randomised, blinded, placebo-controlled, 4-way crossover study in 32 healthy volunteers (24 completed the study and 1 received placebo and ebastine but not terfenadine). Serial ECGs and blood samples were taken at predose and 2, 3, 4, 5, 6, 8 and 12 hours postdose on days –1 (baseline) 5, 6 and 7

Treatment	No. of volunteers	QTc mean		QTc maximum		QTc AUC_{0-12h}	
		baseline mean	mean change (SEM)	baseline mean	mean change (SEM)	baseline mean	mean change (SEM)
Placebo	25	383.8	1.4 (2.5)	402.0	0.7 (3.4)	4609.0	13.2 (30.6)
Ebastine 60mg qd	24	384.8	3.7 (2.5)††	403.3	2.2 (3.5)†	4613.0	49.9 (31.4)††
Ebastine 100mg qd	25	380.9	10.3 (2.5)**†	399.3	8.2 (3.4)*	4570.9	124.2 (30.6)**†
Terfenadine 180mg bid	24	382.7	18.0 (2.5)***	402.7	13.3 (3.5)**	4590.4	213.8 (31.4)***

bid = twice daily; **qd** = once daily.

* $p < 0.05$,** $p < 0.01$, *** $p < 0.001$ versus placebo; † $p < 0.05$, †† $p < 0.001$ versus terfenadine.

7 days (recommended dosage is 60mg twice daily), in a 4-way randomised crossover design with 32 healthy volunteers.[15] Serial ECGs were conducted at baseline and on days 5, 6 and 7 of administration, and the results are summarised in table II. There was no statistically significant difference in the mean QTc interval change from baseline between ebastine 60 mg/day (+3.7 msec) and placebo (+1.4 msec), whereas the difference reached statistical significance for terfenadine (+18.0 msec) versus placebo and versus ebastine. Ebastine 100 mg/day had a small effect on the mean QTc interval (+10.3 msec), which, although statistically significant versus placebo, was not clinically relevant and was significantly less than the mean QTc prolongation observed with terfenadine. Similar relationships were found when maximum QTc intervals were considered. Increases in the mean QTc interval of greater than 10% occurred in 4 of 24 (17%) participants who received terfenadine 360 mg/day, but not in any of those receiving 60 or 100 mg/day of ebastine. There were no reports of dysrhythmias or changes in ECG morphology in those who received high doses of ebastine, nor with the positive control terfenadine dose.

Linear regression analysis demonstrated a statistically significant relationship between increasing ebastine and carebastine plasma concentrations and QTc interval changes from baseline, although the relationship appeared to plateau at the higher concentrations. Mean estimates of pharmacokinetic parameters for ebastine following administration of 60 mg/day for 7 days ranged from 43.9 to 316.2 (mean 134.3) μg/L • h for the area under the concentration *vs* time curve for the first 24 hours (AUC_{0-24h}); from 2.8 to 65.8 (mean 22.1) μg/L for maximum plasma concentrations (C_{max}); from 0 to 3.2 (mean 1.3) μg/L for minimum steady-state concentrations (C_{min}); and from 2 to 5 (mean 2.7) hours for t_{max}. Corresponding data for ebastine 100 mg/day ranged from 24.0 to 569.8 (mean 286.5) μg/L • h for AUC_{0-24h}; from 1.4 to 86.1 (mean 46.4) μg/L for C_{max}; from 0 to 6.0 (mean 2.6) μg/L for C_{min}; and from 2 to 5 (mean 2.9) hours for t_{max}.

For carebastine, the mean estimates of pharmacokinetic parameters following administration of ebastine 60 mg/day for 7 days ranged from 3269.2 to 16 467 (mean 9350.1) μg/L • h for AUC_{0-24h}; from 168.9 to 891.9 (mean 508.5) μg/L for C_{max}; from 0 to 444.5 (mean 262) μg/L for C_{min}; and from 2 to 12 (mean 5.3) hours for t_{max}. Following administration of ebastine 100 mg/day for 7 days, the mean estimates for carebastine ranged from 4007.7 to 29 537 (mean 14 007) μg/L • h for AUC_{0-24h}; from 210.2 to 1818.7 (mean 774.4) μg/L for C_{max}; from 0 to 904.5 (mean 440.9) μg/L for C_{min}; and from 0 to 12 (mean 5.5) hours for t_{max}.

3.2 Interaction with Ketoconazole (Single and Multiple Doses)

In the single dose interaction study,[16] ebastine (20mg) was given on days 1 and 9 of a 13-day

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protocol and ketoconazole (400 mg/day) was administered on days 4 through to 12. ECGs (12 leads) were performed at screening, on admission (day –2), and on days 10, 11, 12 and 13. Serial ECGs (3 leads) up to 24 hours were performed on admission (day –2), at baseline (day –1), and on days 1, 8 and 9. Holter monitoring was performed for 24 hours at screening on day 1 and for 48 hours beginning on day 8. Telemetry was performed on days 1 and 9. No clinically relevant changes in QTc interval were observed following the coadministration of the 2 drugs and there were no clinically relevant findings on Holter monitoring and during telemetry.

Mean plasma concentrations of ebastine measured on day 9 peaked at 42 μg/L at 4.5 hours (not detectable on day 1), and the 6-hour peak (135 μg/L) of carebastine on day 1 was changed to a 50 to 60 μg/L plateau extending from 8 to 96 hours.

There was no relationship between plasma concentrations of either ebastine or carebastine and either absolute QTc or change from baseline.

The multiple dose study[17] assessed the interaction effects at steady state after administration of ebastine 20 mg/day or placebo alone for 5 days, and after coadministration with 400 mg/day of ketoconazole for an additional 8 days. ECGs were performed serially (–0.5 and +1, 2, 4, 6, 8 and 12 hours postdose) on days –1, 5 and 13. Telemetry was performed from days 6 to 14 and additional ECGs were obtained on day 6 to 12, 15 to 18, and 20 and 22. The coadministration of ketoconazole 400 mg/day with ebastine 20 mg/day caused a statistically significant mean QTc interval prolongation of 18.1 msec when compared with placebo (8.0 msec). The results are summarised in table III. There were no clinically relevant findings during telemetry.

After 8 days of coadministration of ketoconazole (400 mg/day) with ebastine 20 mg/day, the steady-state pharmacokinetic parameters for unmetabolised ebastine were significantly different from those observed following administration of ebastine 20 mg/day alone for 5 days. Thus, the C_{max} of ebastine increased approximately 15-fold (3.75 to 58.95 μg/L), C_{min} increased approximately 70-fold (0.19 to 14.85 μg/L), and the AUC increased by approximately 40-fold (17.92 to 761.59 μg/L • h) in the presence of ketoconazole. The pharmacokinetics of carebastine were less affected by ketoconazole coadministration, with relatively no changes observed in C_{max} (from 344.62 to 384.19 μg/L) and a slight increase in C_{min} (145.3 to 333.8 μg/L) and AUC (5688.4 to 8192.2 μg/L • h). Serum elimination half-life ($t_{½\beta}$) increased from 6.4 to 87.7 hours for ebastine and from 24.6 to 80.6 hours for carebastine following ketoconazole coadministration. Linear regression analysis of mean QTc interval changes versus mean and maximum plasma ebastine concentrations showed a statistically significant relationship between increasing plasma ebastine concentrations and QTc interval changes from baseline. Nevertheless, this relationship showed a clear trend to plateau (≈15

Table III. The influence of concomitant administration of ketoconazole (400 mg/day) from day 6 to day 15 on the effects of placebo and ebastine (20 mg/day) from day 1 to day 15 on the mean, maximum and area under the curve for the first 12 hours (AUC_{0-12h}) QTc intervals (msec) in healthy volunteers. Serial ECGs and blood samples were taken at predose and 1, 2 and then every 2 hours up to 12 hours postdose on day –1 (baseline), day 5 (end of monotherapy) and day 13 (end of combination therapy)

	QTc mean		QTc maximum		QTc AUC_{0-12h}	
	ebastine	placebo	ebastine	placebo	ebastine	placebo
Day –1 (n = 27/28)	383.8	384.0	402.6	399.5	4605.0	4609.2
Day 5 (ebastine alone) [n = 27/26]	383.0	383.5	397.9	398.9	4561.6	4600.1
Day 13 (ebastine + ketoconazole) [n = 26/26]	401.2	391.4	418.3	407.2	4821.7	4700.7
Day 13 minus day 5 (SEM)	18.1 (2.5)*	8.0 (2.3)	19.9 (3.4)*	8.3 (2.8)	231.0 (31.8)*	100.6 (27.4)

* $p < 0.001$ for one-sided test of difference between ebastine and placebo (n = 26/26).

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msec) at 25 μg/L, such that higher concentrations were not accompanied by further concentration-related increases in the QTc interval.

One volunteer was observed to have morphological abnormalities in the ECG (increased U wave and somewhat flattened T waves) during coadministration of ebastine and ketoconazole, although these also appeared to have been present prior to administration of the study medications. Also, when this volunteer was rechallenged with placebo and ketoconazole, these same abnormalities recurred and therefore do not appear to be related to the administration of ebastine. No placebo/ketoconazole recipients exhibited a mean QTc increase of greater than 10%; however, one ebastine/ketoconazole recipient exhibited a mean QTc increase of 63 msec from baseline to day 13. During rechallenge with placebo/ketoconazole, this individual demonstrated a 22 msec increase in QTc, and a review of his ECG data showed that the 63 msec change does not represent an unusual response or one that differs from the response observed among all the participants in the study. Nevertheless, it is also important to note that on the day of screening for recruitment his single ECG showed an uncorrected QT of 467 msec, which was reduced to a QTc of 419 msec as a consequence of a relatively slow heart rate (48 beats/min). Corresponding mean values for QT, QTc and heart rate from the 6 postdose serial ECGs on day –1 (baseline), day 5 and day 13 were 403 msec, 388 msec and 55 beats/min, 390 msec, 390 msec and 60 beats/min, and 413 msec, 451 msec and 72 beats/min, respectively, showing that most of the 63 msec increase in QTc from baseline was driven by an increase in heart rate from below 60 beats/min to above this value.

3.3 Interaction with Erythromycin (Single and Multiple Doses)

In the single dose portion of an interaction study,[18] ebastine (20mg) was given to 15 volunteers on days 1 and 9 of a 13-day protocol and erythromycin stearate (500mg daily) was administered on days 4 to 12. ECGs (12 leads) were obtained at screening, on admission (day –2) and on days 10, 11, 12 and 13. Serial ECGs (3 leads) were performed at baseline (day –1) and on days 1, 8 and 9. Telemetry was performed on days 1 and 9. Holter monitoring was performed in all participants for 24 hours at screening and on day 1, and for 48 hours beginning on day 8. Results showed no clinically relevant changes in the QTc interval following coadministration of the 2 drugs, and there were no clinically relevant findings on Holter monitoring and during telemetry.

Ebastine plasma concentrations were below the level of detection (20 μg/L) following single dose administration. By contrast, after coadministration with erythromycin at steady state, 10 of 15 volunteers had sporadically measurable plasma ebastine concentrations (21.0 to 43.6 μg/L). Mean plasma levels of carebastine peaked at 186 μg/L (5.13 hours) on day 1 and at 227 μg/L (9.8 hours) on day 9, with a corresponding prolongation of elimination ($t_{½}$ increased from 18.2 to 32.2 hours) and an increase in AUC from zero to infinity (AUC_{∞}) from 5269 to 13 053 μg/L • h.

There was no relationship between plasma concentrations of carebastine and either absolute QTc or change from baseline.

In the multiple dose interaction study,[19] the following were administered for 10 days in crossover fashion: ebastine 20 mg/day + placebo; ebastine 20 mg/day + erythromycin ethylsuccinate (800mg 3 times daily); and placebo + erythromycin ethylsuccinate (800mg 3 times daily). In each treatment period, 12-lead ECGs were performed serially (predose, 1 hour, 2 hours and every 2 hours) up to 12 hours on day –1 (baseline) and day 10. ECGs (12 leads) were also performed at 6 hours after the morning dose on days 1 to 5, at 6 and 12 hours on days 6 to 9, and on days 11 to 16. Continuous telemetry was performed on days 1 to 12. Coadministration of ebastine with erythromycin ethylsuccinate resulted in a statistically significant prolongation of the mean QTc interval of 19.6 msec compared with ebastine alone (6.1 msec), or erythromycin alone (8.9 msec) (table IV). Increases in the mean QTc interval >10% over baseline occurred in 2 (8%)

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Table IV. The influence of 10 days' concomitant administration of erythromycin ethylsuccinate (800mg 3 times daily) on the effects of placebo and ebastine (20mg) on the mean, maximum and area under the curve for the first 12 hours (AUC_{0-12h}) QTc intervals (msec) in volunteers, according to a crossover design. Serial ECGs and blood samples were taken predose and 1, 2 and then every 2 hours up to 12 hours postdose on day –1 (baseline) and day 10

Schedule	n	QTc mean		QTc maximum		QTc AUC_{0-12h}	
		baseline	mean change (SEM)	baseline	mean change (SEM)	baseline	mean change (SEM)
Ebastine/placebo	27	387.88	6.11 (1.98)**†‡	411.07	2.43 (3.25)**†	4634.78	96.6 (23.71)**†‡
Erythromycin/placebo	28	391.61	8.9 (1.93)**‡	412.25	9.41 (3.17)*‡	4686.47	109.43 (23.14)**†‡
Ebastine/erythromycin	25	389.83	19.6 (2.12)	408.76	22.34 (3.50)	4660.54	242.63 (25.42)

* $p < 0.005$, ** $p < 0.0001$ for differences from ebastine/erythromycin group; † $p > 0.01$ for nonsignificant difference from ebastine/erythromycin; ‡ $p < 0.002$ for differences from baseline.

volunteers while receiving the combination of ebastine and erythromycin, but not with either drug administered alone. One volunteer had a mean QTc interval increase of 41 msec (10.9%) on day 10 of ebastine/erythromycin ethylsuccinate administration (mean baseline QTc = 376 msec) and another had a mean QTc interval increase of 39 msec (10.5%) on day 10 of ebastine/erythromycin ethylsuccinate administration (mean baseline QTc = 373 msec). There were no reports of dysrhythmias or changes in ECG morphology in volunteers who received the combination of ebastine and erythromycin. No cardiac adverse events were detected during continuous telemetry.

After 10 days of erythromycin and ebastine coadministration, the C_{max} for the ebastine parent compound increased approximately 2-fold (from 8.5 to 18.6 μg/L), accompanied by an approximate 3-fold increase in C_{min} (from 0.41 to 1.2 μg/L), versus ebastine administered alone. Furthermore, the AUC_{0-24h} value was significantly greater (42.8 *vs* 113.0 μg/L • h) following the 10 days of erythromycin coadminstration, demonstrating that concomitant erythromycin increases the extent of ebastine exposure by approximately 2.6-fold. There was no change in t_{max} (2.2 *vs* 2.3 hours). The coadministration of erythromycin caused similar changes in the pharmacokinetics of carebastine. Both AUC_{0-24h} and C_{max} values for carebastine were increased 2- to 3-fold during the coadministration period compared with those for ebastine 20 mg/day alone (from 5033 to 13 237 μg/L • h and from 315.6 to 688.3 μg/L, respectively). There was a small increase in t_{max}, from 5.1 to 6.8 hours. Since erythromycin administration was related to both prolonged QTc interval and to increased concentrations of ebastine and carebastine, and since the range of plasma concentrations was narrow and the combined effects on the QTc were small, pharmacokinetic/pharmacodynamic analysis was unable to separate the effects of erythromycin on the QTc from those possibly due to increased concentrations of ebastine and carebastine.

4. Cardiac Tolerability Data in Special Populations

QTc data were also obtained from the pharmacokinetic studies in special subpopulations, including the elderly, patients with moderate or severe renal insufficiency or hepatic insufficiency, and in children aged 6 to 12 years.[20-24]

4.1 Elderly

Ebastine 10mg was administered once daily for 10 days to 19 healthy elderly participants aged 65 to 82 years and 19 young adults aged 18 to 35 years.[20] In each group, 10 participants received ebastine and 9 received placebo. ECGs were measured at baseline, on days 1, 5 and 10 at 4 to 5 hours postdose and at the end of the study. Ebastine 10mg showed no clinically relevant electrocardiographic effects in healthy young or elderly adults. The incidence of electrocardiographic events on Holter monitoring data was similar in the placebo and ebastine groups in both the young and the elderly participants. There were no statistically significant differences in mean AUC, C_{max} and $t_{½}$ values, in-

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dicating similar pharmacokinetic profiles in young and elderly participants.

4.2 Renal Insufficiency

A single dose of ebastine 10mg was administered to 12 patients with moderate renal insufficiency (creatinine clearance of 1.8 to 3.6 L/h/1.73m^2) and 12 volunteers with normal renal function (creatinine clearance 5.1 to 8.1 L/h/1.73m^2).[21] ECGs were performed at baseline and at 4 and 7 hours postdose. Ebastine 10mg had no clinically relevant electrocardiographic effects in patients with moderate renal insufficiency. No statistically significant differences were noted between patients with renal impairment and healthy volunteers in the mean values for the different pharmacokinetic parameters of carebastine, except for t_{max}, which was significantly greater in renally impaired patients.[25] Mean plasma half-life was longer in patients with renal insufficiency, but the difference with respect to normal participants did not reach statistical significance (26 versus 19 hours).

The effect of ebastine on the QTc interval was also studied in 10 patients with severe renal insufficiency (creatinine clearance ≤1.8 ml/min/1.73m^2) and 10 volunteers with normal renal function.[22] ECGs were obtained at baseline and at 4 and 72 hours postdose. After a single dose of ebastine 20mg, no clinically relevant electrocardiographic effects were seen in individuals with normal renal function or in patients with severe renal insufficiency. A high degree of intrasubject variability in the QTc interval was observed. Estimates of carebastine AUC_∞, C_{max} and t_{max} were not statistically different for patients with severe renal impairment compared with healthy volunteers. A relatively higher apparent volume of distribution for carebastine was noted in the group with renal impairment compared with normal volunteers. This may have been responsible, in part, for the longer $t_{½\beta}$ (23 versus 17 hours in healthy volunteers).

4.3 Hepatic Insufficiency

Ten healthy volunteers and 10 patients with cirrhosis confirmed by histological findings from liver biopsy received a single dose of ebastine 10mg.[23] ECGs were obtained at baseline and at 4 and 72 hours postdose. Results showed no clinically relevant differences in ECG findings between the 2 groups. AUC and C_{max} values for carebastine in patients with liver cirrhosis were not statistically different from those in the healthy volunteers.[26] However, carebastine $t_{½\beta}$ in the patients with hepatic impairment was significantly longer than in healthy volunteers (27 versus 19 hours). A trend towards a higher apparent volume of distribution was also noted in the hepatically impaired patients, possibly as a result of lower concentrations of plasma binding proteins (albumin). This relatively higher volume of distribution may have been responsible for the observed longer $t_{½\beta}$ of carebastine.

Ebastine was not detected in any of the plasma samples collected at predose through 72 hours postdose.

4.4 Children

In a single-centre cardiac tolerability study, 28 children (aged 6 to 11 years) received either 15mg of ebastine syrup (n = 14) or placebo (n = 14) for 6 days.[24] ECGs were performed serially up to 8 hours on days 1, 3 and 6, and Holter monitoring was carried out at screening and on days 1 and 6. Telemetry was performed during the first 12 hours after drug administration on day 1 and from day 4 through the morning of day 7. Telemetry also was performed in the evening on days 1, 2 and 3. Ebastine 15mg had no clinically relevant effect on the QTc interval duration compared with placebo. No electrocardiographic effects were seen on ECG, Holter monitoring or telemetry.

5. Other Pharmacokinetic/ Pharmacodynamic Studies

QTc data were also obtained from other pharmacokinetic/pharmacodynamic studies in which a

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single dose of ebastine was administered.[27-31] QTc values were measured as follows:

- on days 6 and 10 of each study period in a pharmacokinetic study conducted to assess the interaction of ebastine 20mg with theophylline 400mg twice daily[27]
- at baseline and at 4 and 72 hours postdose in a pharmacokinetic food interaction study with a single dose of ebastine 10mg[28]
- serially up to 72 hours in a pharmacokinetic food interaction study with a single dose of ebastine 20mg[29]
- at baseline and at 4 and 72 hours postdose in a pharmacodynamic study that evaluated the effect of single doses of ebastine up to 30mg on histamine skin response[30]
- serially during the first 8 hours in a pharmacodynamic study that assessed the antimuscarinic activity of a single doses of ebastine 10, 20 and 30mg.[31]

Results from these studies demonstrate that a single dose of ebastine 20mg with theophylline and single doses of ebastine 10 and 20mg with and without food had no clinically relevant electrocardiographic effects. Similarly, administration of a single dose of ebastine up to 30mg in healthy volunteers had no clinically relevant effect on the QTc interval.

In the food interaction studies,[32] the $AUC_{0\text{-}4h}$ was 40 to 50% higher and C_{max} was approximately 40% higher under fed compared with fasting conditions. The t_{max} and $t_{½\beta}$ were not affected by food. The observed increase in carebastine plasma concentrations with food is not expected to be of any concern with regard to clinical tolerability, since the observed concentrations were considerably below those observed in the high dose cardiac tolerability study. In clinical trials, where it was administered both with and without food, ebastine was found to be both effective and well tolerated.

6. Cardiac Tolerability of Ebastine in Relation to Other Antihistamines

Terfenadine and astemizole are associated with a considerably higher risk of cardiovascular toxicity than ebastine. There are several reports to show that terfenadine and astemizole at the recommended dose, under conditions of inhibited metabolism or in overdose, are associated with a clinically significant QTc interval prolongation that leads to life-threatening torsade de pointes or death.[33-35] In the high dose clinical pharmacology study already described, ebastine, at 10 to 5 times the recommended doses of 10 and 20mg, had a significantly smaller effect (10 msec) on QTc interval prolongation than terfenadine 180mg twice daily (3 times the recommended dose) [18 msec] and, at 6 to 3 times the recommended dose, ebastine (60mg) was without effect on QTc (3.7 msec).

The QTc interval prolongation attributable to the interaction of ebastine with ketoconazole is small compared with that of the concomitant administration of terfenadine with ketoconazole. Honig et al.[36] have shown a mean increase in the QTc interval of 82 msec (mean QTc 490 ± 16 msec) following coadministration of 400 mg/day (200mg twice daily) of ketoconazole with 120 mg/day (60mg twice daily) of terfenadine. In that study, all 6 participants developed abnormal morphology of the TU complex, which is more definitively associated with an increased risk of torsade de pointes, and in 4 participants administration of ketoconazole had to be stopped before the completion of the study for safety reasons. ECGs remained abnormal for up to 72 hours after the last dose of terfenadine. In the interaction of ebastine with ketoconazole, the addition of 400 mg/day of ketoconazole to 20mg of ebastine caused a mean QTc interval prolongation of 18.1 msec (mean QTc 401 ± 3.1 msec) compared with 8.0 msec (mean QTc 391 ± 3.4 msec) for placebo plus 400 mg/day of ketoconazole. Furthermore, no morphological changes in the ECG due to ebastine were observed in this study.

It is of interest that the change in the QTc interval following the interaction of ebastine with ketoconazole is comparable to that published for cetirizine,[37] when cetirizine 20mg was coadministered with ketoconazole 400 mg/day. Accordingly, the combination of cetirizine and ketoconazole caused a QTc interval prolongation of 17.4

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msec; the effect of cetirizine alone was 9.1 msec and, in the absence of evidence for a pharmacokinetic interaction, the combined effect is considered to be additive.

Ebastine and terfenadine also differ in their pharmacokinetic-pharmacodynamic relationships, which indicate that ebastine has a much lower potential for cardiovascular effects. An integrated pharmacokinetic/pharmacodynamic analysis using a population approach (NONMEM program) was performed to examine the relationship between plasma ebastine (parent compound) concentrations and QTc changes.[38] Pooled data from the high dose study (60 mg/day, 100 mg/day ebastine) and the ketoconazole interaction study (20 mg/day ebastine + 400 mg/day ketoconazole) were used to assess the relationship between mean ebastine plasma concentrations and resultant mean QTc interval changes and the effect of ketoconazole on this relationship. The analysis demonstrated that a relationship exists between increasing ebastine plasma concentrations and QTc interval changes, but also that this relationship plateaus at approximately 15 msec, such that further increases in ebastine plasma concentrations are not accompanied by further increases in the QTc interval.

Honig et al.,[36] on the other hand, found a strong linear correlation between plasma terfenadine concentrations and the magnitude of change in the QTc interval when ketoconazole was coadministered with terfenadine, with no plateau effect at higher concentrations. Morganroth et al.[39] have also reported a linear dose-response relationship between the change in QTc and increasing doses of terfenadine, with a slope of 0.128 msec/mg. The QTc increased by 5 to 10 msec with terfenadine at a dose of 60mg twice daily, by 20 to 25 msec with 180mg twice daily (3 times the recommended dose), and a study using a dose of 300mg twice daily (5 times the recommended dose) was abandoned for safety reasons. A retrospective analysis of the literature made by the same authors revealed 20 patients who had received this latter dose and experienced a mean increase in QTc of 42 msec.[39]

7. Conclusions

In terms of cardiac tolerability, ebastine has been the most extensively studied and characterised antihistamine when compared with other marketed antihistamines. The overall cardiac tolerability profile based on available information to date suggests that ebastine, like loratadine and cetirizine, has a lower potential for causing adverse cardiovascular effects compared with terfenadine and astemizole. At the recommended dosages of 10 and 20mg once daily, ebastine has no effect on the QTc interval. Moreover, ebastine has no clinically relevant effect on the QTc interval in special populations (the elderly, patients with renal or hepatic insufficiency, and children aged 6 to 12 years). Even when coadministered with ketoconazole or erythromycin, or when given at 5 to 10 times the recommended doses of 10 and 20mg, the total QTc effect is only about 10 msec, a clinically non-meaningful change and, even more importantly, is not related to dosage or plasma concentrations.

Nevertheless, although ebastine itself has no clinically meaningful effect on the QTc interval even at high plasma concentrations, the fact that ketoconazole and erythromycin have been shown to increase the QTc interval when administered alone (together with reports of arrhythmias with other 'safe' antihistamines[40]) has led a panel of expert cardiologists[41] to recommend the inclusion of a precautionary statement in the labelling regarding the use of ebastine in patients known to have the following conditions: long QTc syndrome, hypokalaemia, treatment with any drug known to produce an increase in the QTc interval or inhibit cytochrome P450 3A4, such as azole antifungals and macrolide antibacterials. This warning should stand at least until there are sufficient postmarketing surveillance data on ebastine to warrant otherwise.

8. Addendum

A recently completed study of the effects of loratadine (10mg once daily) on the QTc interval when coadministered with ketoconazole, which

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Table V. Comparison of the effects of 7 days' administration of placebo, ebastine and terfenadine on the mean (SEM) changes in the QT, QTc (Bazett), QTc (Fridericia) intervals (all in msec) and heart rate. Serial ECGs were performed as in table II

Treatment	n	Change in QT	Change in QTc (Bazett)	Change in QTc (Fridericia)	Change in heart rate (beats/min)
Placebo	25	–8.9 (2.4)	1.4 (2.5)	–2.1 (2.1)	3.5 (1.0)
Ebastine 60mg	24	–17.0 (2.5)††	3.7 (2.5)††	–3.2 (2.1)††	7.6 (1.0)*†
Ebastine 100mg	25	–15.2 (2.4)††	10.3 (2.5)*†	1.5 (2.1)††	9.3 (1.0)**††
Terfenadine	24	6.0 (2.5)**	18.0 (2.5)**	14.1 (2.1)**	4.1 (1.0)

* $p < 0.01$, ** $p < 0.001$ versus placebo; † $p < 0.05$, †† $p < 0.001$ versus terfenadine.

followed an essentially identical protocol to that used with ebastine as described in this review, has shown a statistically significant increase in mean QTc of 16.3 msec, compared with an increase of 9.6 msec with ketoconazole plus placebo.[42]

The remarkable similarity in the total pharmacodynamic effect of ketoconazole plus ebastine (marked pharmacokinetic interaction), loratadine (moderate pharmacokinetic interaction), or cetirizine (no pharmacokinetic interaction) suggests that the effect of ketoconazole is something more than simple inhibition of antihistamine metabolism.

Furthermore, an evaluation of the effects of placebo, ebastine (60mg once daily and 100mg once daily) and terfenadine (180mg twice daily) on the uncorrected QT and the QTc corrected by Fridericia's formula instead of Bazett's formula, as used for the values quoted in this review, has shown that ebastine actually shortens the uncorrected QT interval and that when corrected by Fridericia's formula there is no change from placebo.

By contrast, terfenadine still shows a significant increase in the uncorrected QT interval, which persists following correction by Fridericia's formula (table V).

These observations find explanation in the small but statistically significant increase in heart rate (4 to 6 beats/min) associated with ebastine administration, which is not seen with terfenadine, and in the consequent overcorrection of the QTc induced by Bazett's formula under these conditions; for this reason, Fridericia's formula is considered to be more useful and to be preferred for measuring the effects of drugs on the duration of repolarisation.[43]

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